• BRIEF REPORTS •

Patients with brain metastases from gastrointestinal tract cancer treated with whole brain radiation therapy: Prognostic factors and survival

Susanne Bartelt, Felix Momm, Christian Weissenberger, Johannes Lutterbach

Susanne Bartelt, Department of Radiation Oncology, University of Freiburg, Freiburg i. Br., Germany
Felix Momm, Department of Radiation Oncology, University of Freiburg, Freiburg i. Br., Germany
Christian Weissenberger, Department of Radiation Oncology, University of Freiburg, Freiburg i. Br., Germany
Johannes Lutterbach, Department of Radiation Oncology, University of Freiburg, Freiburg i. Br., Germany
Correspondence to: Susanne Bartelt, M.D., Radiologische Universitätsklinik, Abteilung Strahlenheilkunde, Robert-Koch Strasse 3, 79106 Freiburg, Germany. bartelt@mst1.ukl.uni-freiburg.de
Telephone: +49-761-270-9462   **Fax:** +49-761-270-9582
Received: 2004-02-27   **Accepted:** 2004-04-14

Abstract

AIM: To identify the prognostic factors with regard to survival for patients with brain metastasis from primary tumors of the gastrointestinal tract.

METHODS: Nine hundred and sixteen patients with brain metastases, treated with whole brain radiation therapy (WBRT) between January 1985 and December 2000 at the Department of Radiation Oncology, University Hospital Freiburg, were analyzed retrospectively.

RESULTS: Fifty-seven patients presented with a primary tumor of the gastrointestinal tract (esophagus: $n = 0$, stomach: $n = 10$, colorectal: $n = 47$). Twenty-six patients had a solitary brain metastasis, 31 patients presented with multiple brain metastases. Surgical resection was performed in 25 patients. WBRT was applied with daily fractions of 2 Gray (Gy) or 3 Gy to a total dose of 50 Gy or 30 Gy, respectively. The interval between diagnoses of the primary tumors and brain metastases was 22.6 mo *vs* 8.0 mo for patients with primary tumors of the colon/rectum *vs* other primary tumors, respectively ($P<0.01$, log-rank). Median overall survival for all patients with brain metastases ($n = 916$) was 3.4 mo and 3.2 mo for patients with gastrointestinal neoplasms. Patients with gastrointestinal primary tumors presented significantly more often with a solitary brain metastasis than patients with other primary tumors ($P<0.05$, log-rank). In patients with gastrointestinal neoplasms ($n = 57$), the median overall survival was 5.8 mo for patients with solitary brain metastasis *vs* 2.7 mo for patients with multiple brain metastases ($P<0.01$, log-rank). The median overall survival for patients with a Karnofsky performance status (KPS) ⩾70 was 5.5 mo *vs* 2.1 mo for patients with KPS <70 ($P<0.01$, log-rank). At multivariate analysis (Cox Model) the performance status and the number of brain metastases were identified as independent prognostic factors for overall survival.

CONCLUSION: Brain metastases occur late in the course of gastrointestinal tumors. Pretherapeutic variables like KPS and the number of brain metastases have a profound influence on treatment outcome.

INTRODUCTION

The metastatic dissemination of a solid tumor to the brain is generally associated with a poor prognosis[1]. The most common primary tumors metastasizing to the brain are breast and lung cancer, whereas patients with other primary tumors, e.g. tumors of the gastrointestinal tract, rarely present with brain metastases[2-4]. Furthermore, within the group of gastrointestinal tumors, the incidence of brain metastases shows notable differences. They are extremely rare in esophageal tumors[5,6], but more common in rectal cancer. Few literatures concerning this group of patients are available and therefore prognosis and hence treatment strategies remain controversial.

We retrospectively evaluated patient-, tumor- and treatment-related variables in patients with brain metastases of primary tumors of the gastrointestinal tract (i.e. epithelial tumors of the esophagus, stomach, colon, sigma, and rectum) who were treated with whole brain radiation therapy (WBRT) at our institution. The aim of the study was to identify the prognostic factors with regard to the endpoint survival.

MATERIALS AND METHODS

The records of all patients with brain metastases, who were treated with WBRT at our institution between January 1985 and December 2000, were analyzed retrospectively. Brain metastases were detected by contrast-enhanced cerebral computed tomography (CT) ($n = 43$) or magnetic resonance imaging (MRI) ($n = 14$).

WBRT was performed in 16 patients with cobalt[60] gamma rays, and in 41 patients with 6 MV photons of a linear accelerator. During the study period two fractionation schemes were used: conventional fractionation with daily fractions of 2 Gray (Gy), five days per week to a planned total dose of 50 Gy ($n = 42$) and since 1997 hypofractionation with daily fractions of 3 Gy, five days per wk to a planned total dose of 30 Gy ($n = 15$). None of the patients underwent a chemotherapy during WBRT.

The recursive partitioning analysis (RPA) was used to classify the patients with brain metastases[7]. Class I contained all patients with a Karnofsky performance status (KPS ⩾70, age < 65 years, a controlled primary tumor and no extracerebral metastases), Class III contained all patients with a KPS <70, and Class II contained all other patients.

All patients alive at the time of analysis were censored with the date of last follow-up. The endpoint of the study was overall survival. Survival was calculated from the first day of radiotherapy using the method of Kaplan and Meier. Survival curves were compared using the log-rank test. All factors with a P-value ⩽0.1 at univariate analysis were entered into a multivariate analysis using the proportional hazards model.

RESULTS

Patient characteristics

Fifty-seven (6.2%) of the 916 patients presented with brain metastases from a cancer of the gastrointestinal tract. The exact localization of the primary tumor is shown in Table 1. None of the patients had an esophageal tumor, the most common primary site was rectum ($n = 24$) and colon/sigma ($n = 23$). In all patients, histology obtained either from the primary tumor, brain metastases or from extracerebral metastases, was adenocarcinoma.

Table 1 Site of primary tumor within gastrointestinal tract[1]

Site of primary tumor	n (%)
Esophagus	0 (0)
Stomach	10 (17.5)
Colon	17 (30)
Sigma	6 (10.5)
Rectum	24 (42)

[1]Esophagus, stomach, colon, sigma, rectum.

Thirty patients were males, 27 females. Their median age at diagnosis was 65 years (range: 30-80 years). Twenty-nine patients (51%) had a KPS $\geqslant$70. Twenty-six patients (46%) had a solitary brain metastasis, 31 (54%) had multiple lesions. Location of the metastases is shown in Table 2. Gross total resection was performed in 25 patients (19 patients with single metastasis, six patients with multiple metastases).

Table 2 Location of brain metastases

Location	n (%)
Single lesion	26 (100)
Frontal	4 (15)
Temporal	1 (4)
Parietal	6 (23)
Occipital	1 (4)
Cerebellum	14 (54)
Brainstem	0 (0)
Multiple lesions	31 (100)
Supratentorial	20 (64)
Infratentorial	3 (10)
Both	5 (16)
Unknown	3 (10)

All patients presented with extracerebral metastases, mostly of the lung and/or the liver. Grouped according to the RPA classes, none of the patients met the criteria for class I. Twenty-nine patients (51%) met the criteria for class II. Twenty-eight patients (49%) presented with a KPS <70, and therefore belonged to RPA class III.

Patients with a primary tumor of the gastrointestinal tract presented with a solitary brain metastasis significantly more often (46%) than patients with other primary tumors (30%) ($P < 0.05, \chi^2$). In patients with a primary tumor of the gastrointestinal tract, 25% (14 of 43 patients) had a solitary metastasis localized in the cerebellum, whereas the localization of solitary metastases in the cerebellum in patients with other primary tumors was 5% (42 of 805 patients). This difference was statistically significant ($P < 0.01$). Other locations of brain metastases were not significantly different between these two groups.

The time from the diagnosis of primary tumors to the diagnosis of brain metastases was 16.3 mo, 27 mo, and 20 mo in patients with gastric carcinoma, colon carcinoma , and rectum carcinoma, respectively, and showed no statistically significant difference. Compared with patients with other primary tumors, patients with primary tumors of the colon/rectum had a significant longer interval between the diagnoses of primary tumors and brain metastases (22.6 mo vs 8.0 mo, respectively, $P<0.01$).

Survival data

The median overall survival (OS) time for patients with a primary tumor of the gastrointestinal system was 3.2 mo and showed no significant difference compared to the overall survival time of 3.5 mo for patients with brain metastases and other primary tumors (Figure 1). OS rate for patients with gastrointestinal tumors was 49%, 30%, and 7%, at 3, 6, and 12 mo, respectively. Within the group of gastrointestinal tumors, patients with a primary tumor of the stomach, colon/sigma, and rectum had a median OS time of 2.7, 5.2, and 3.2 mo, respectively. This was not a statistically significant difference.

Prognostic factors

The potential prognostic factors tested for significance in univariate analysis were sex, age ($\geqslant$/< 65 years), pretherapeutic performance status (KPS $\geqslant$/< 70), number (single vs multiple) and distribution of brain metastases (Table 2), extracerebral tumor activity (yes vs no), resection status (operation yes vs no), and fractionation scheme (conventional fractionation vs hypofractionation). The fractionation scheme (2 Gy daily, 50 Gy total dose vs 3 Gy daily, 30 Gy total dose) showed no statistical significance for OS.

Three factors had a P-value $\leqslant$0.1 in univariate analysis and were entered into multivariate analysis: pretherapeutic performance status, number of brain metastases, and resection status. Concerning the OS, patients with a KPS $\geqslant$70 had a median OS time of 5.5 mo vs 2.1 mo for patients with a KPS < 70 ($P<0.01$) (Figure 2). The same values were found by comparing the patients in RPA class II vs RPA class III. The median OS time for patients with a solitary metastasis was 5.8 mo and 2.7 mo for patients with multiple metastases ($P<0.01$) (Figure 3). The median OS time for patients with resection of brain metastasis was 6.6 mo and 2.7 mo for patients without resection ($P<0.01$).
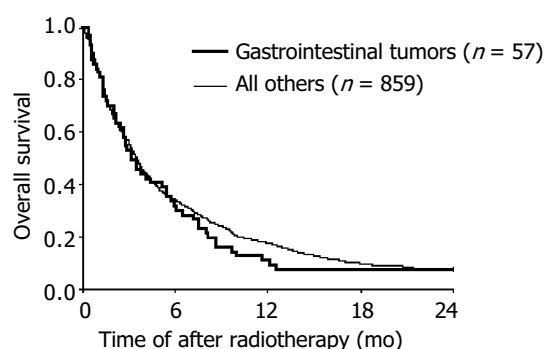
Figure 1 Overall survival according to primary tumor.
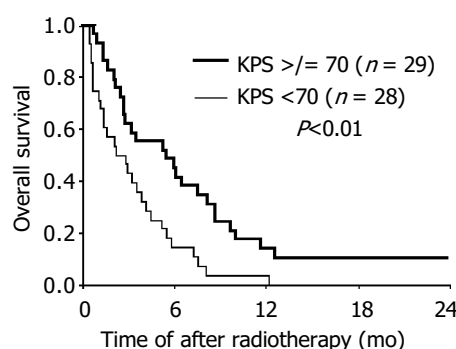
Figure 2 Overall survival according to KPS ($\geqslant$70 vs <70).
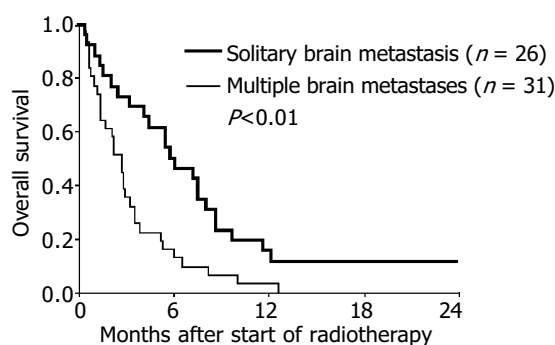
Figure 3 Overall survival according to the number of brain metastases (solitary *vs* multiple).

In the first multivariate model limited to pretherapeutic variables, the number of brain metastases (single *vs* multiple, relative risk [RR] 0.63, 95% confidence interval [KI] 0.45-0.88) and the KPS ($\geq$70 *vs* <70, RR 0.59, 95% KI 0.42-0.82) turned out to be independent prognostic factors. In the second multivariate analysis we added the therapeutic variable 'resection'. The KPS and the number of brain metastases were still independent prognostic factors (RR 0.59, 95% KI 0.43-0.79, P<0.01 and RR 0.65, 95% KI 0.45-0.90, P<0.05 respectively), whereas resection status was not a prognostic factor.

DISCUSSION

In our series, 6.2 % of the patients treated with WBRT presented with a primary tumor located in the gastrointestinal tract. None of the 916 patients had a primary esophageal carcinoma. Brain metastases from esophageal carcinoma were extremely rare, with a reported incidences of approximately 1-5% in autopsy series[8,9], and approximately 1-4% in clinical series[5,6,10,11].

In ten patients the primary tumor was a gastric carcinoma. The majority of publications on brain metastases from gastric carcinoma were case reports[12]. Two large studies found 0.7% of 3 320 patients, and 0.16% of 8 080 patients with gastric carcinoma to have brain metastases[13,14]. In an autopsy series by Poser and Chernik, 5 of 46 patients (10.8%) with gastric carcinoma had brain metastases[2]. The rarity of brain metastases both from esophageal and gastric cancer might result from the grim prognosis of these tumor entities[15]. In esophageal cancer, brain metastases tended to occur in patients with large primary tumors[5], usually implicating a short overall OS time. The low incidence in clinical trials might further result from an inadequate diagnostic evaluation, and symptoms indicating brain pressure like nausea and vomiting might be attributed to the primary tumor[14]. The reason for the relatively high incidence of brain metastases from gastric cancer in our group is not clear. Gastric carcinoma is rare in Europe compared to Asian countries. In half of our patients gastric carcinoma was a gastric cardia carcinoma, and recent studies suggested, that they were distinct from adenocarcinomas of the esophagus and stomach regarding epidemiological and biological factors[16-18]. These differences could possibly be associated with other pathways of metastatic spread, resulting in a relatively higher incidence of brain metastases.

Forty-seven patients had a primary colorectal carcinoma. The incidence of brain metastases in colorectal cancer ranged 2-10% in clinical studies[19-21]. As observed in other studies[14,21,22], the majority of primary tumors in our patients were located in the distal parts of the colon, i.e. sigma and rectum (64%). Significantly more patients with colorectal primary tumors presented with cerebellar metastases compared to patients with other primary tumors (25% *vs* 5%, respectively, P<0.01). Studies by Wronski and Alden confirmed this finding, with a frequency for infratentorial location of 35% and 55%, respectively[21,23]. The relative over-representation of cerebellar metastases in

colorectal carcinoma might be due to tumor spread by way of the vertebral system (i.e. Batson's plexus), bypassing the lungs[24]. The two other possible routes of hematogeneous dissemination of colorectal cancer to the brain were via the rectal vein plexus to the inferior vena cava, bypassing the liver, or via the portal veins to the liver and lung and then to the brain[20,25]. The incidence of pulmonary metastases in our patients with colorectal cancer was 50% (23/46 patients), which was clearly higher than the approximatley 30% for patients with metastatic colorectal cancer[26], an observation also made in others[19-21]. Presumably the rectal plexus of veins, draining into the inferior vena cava and subsequently the lung are also an important route for tumor spread to the brain.

The interval between the diagnosis of primary tumor and brain metastases in our study group for patients with gastric and colorectal carcinoma was significantly longer (22.6 mo) than that for patients with other primary tumors (8.0 mo). Although only few larger studies on patients with colorectal carcinoma and brain metastases are available to date, all reported a late onset of brain metastases, with a period ranging 21-36 mo between detection of primary tumors and diagnosis of brain metastases[19-21,23,27-29] (the larger studies on gastric cancer did not give detailed information on this topic[13,14,30]). Corresponding to the late onset of brain metastases in the clinical course of gastric and colorectal tumors, all of our patients had further extracerebral metastases (consequently none of our patients was qualified for RPA-class I). The high rate of extracerebral metastases was confirmed by most authors[19-23,28,31,32] and even represented the most important prognostic factor in the study of Nieder *et al.*[31].

Although the onset of brain metastases in our patients with gastrointestinal tumors was late, and the systemic disease was advanced, its median OS time was not statistically different from the median OS time of patients with brain metastases of other primary tumors (3.2 *vs* 3.5 mo, respectively). It was comparable to the median OS time for patients with brain metastases and colorectal carcinoma or gastric carcinoma treated with WBRT seen by others, which ranged from 2.0 to 3.6 mo for colorectal carcinoma[20,22,23,32] and approximately 2 mo for gastric carcinoma[13,14]. Hasegawa, in contrary, found a shorter survival time in a radiosurgically treated series of patients with gastrointestinal tumors compared to patients with other primary tumors[27]. Several authors described a longer median OS time of approximately 9 mo for patients who underwent surgical resection of brain metastases as a sole treatment or followed by radiotherapy[21,22,27,32,33]. Whereas resection of brain metastases seemed to be a favorable prognostic factor in our patients in univariate analysis, it was not statistically significant in multivariate analysis.

The independent factors correlated with a better prognosis in our multivariate analysis were a KPS $\geq$70, and the presence of a solitary brain metastasis. It has been widely accepted that the pretherapeutic performance status is one of the most powerful predictive factors for the survival of patients with brain metastases[7,34-38] which could be validated for patients with brain metastases from gastrointestinal tumors in our study group. The more favourable prognosis for patients with primary tumors of the gastrointestinal system presenting with a solitary brain metastasis was also found by Farnell *et al.*[32], whereas others only found the surgical resection of brain metastases to be associated with a better survival[19,23,27]. In our second multivariate analysis, including the therapeutic variable 'resection' status could not be identified as an independent prognostic factor, as mentioned above. In order to diagnose brain metastases in an early phase, in which a resection could still be possible, discrete symptoms hinting cerebral tumor spread should be taken seriously.

A basic problem concerning treatment recommendations for patients with brain metastases of gastrointestinal tumors is that to date only few retrospective studies with a relatively small

number of patients are available. Therefore, the results concerning the prognostic factors should be regarded with caution. The different prognostic factors from each study should be kept in mind when considering a therapeutic concept for individual patients.

In conclusion, brain metastasis is a late event in the course of gastrointestinal tumors, and it occurs later as in patients with other primary tumors. However, the overall survival time is comparable to patients with brain metastases from other primary tumors. Independent prognostic factors in our group were KPS and the number of brain metastases.

REFERENCES

1   Nussbaum E, Djalilian H, Cho K, Hall W. Brain metastases. histology, multiplicity, surgery, and survival. *Cancer* 1996; **78**: 1781-1788

2   Posner J, Chernik N. Intracranial metastases from systemic cancer. *Adv Neurol* 1978; **19**: 579-592

3   Sadahiro S, Suzuki T, Ishikawa K, Nakamura T, Tanaka Y, Masuda T, Mukoyama S, Yasuda S, Tajima T, Makuuchi H, Murayama C. Recurrence patterns after curative resection of colorectal cancer in patients followed for a minimum of ten years. *Hepatogastroenterology* 2003; **50**: 1362-1366

4   Weiss L, Grundmann E, Torhorst J, Hartveit F, Moberg I, Eder M, Fenoglio-Preiser C, Napier J, Horne C, Lopez M. Hematogenous metastatic patterns in colonic carcinoma: an analysis of 1 541 necropsies. *J Pathol* 1986; **150**: 195-203

5   Ogawa K, Takafumi T, Sueyama H, Nobukazu F, Kakinohana Y, Kamata M, Adachi G, Saito A, Yoshii Y, Murayama S. Brain metastases from esophageal carcinoma. *Cancer* 2002; **94**: 759-764

6   Quint L, Hepburn L, Francis I, Whyte R, Orringer M. Incidence and distribution of distant metastases from newly diagnosed esophageal carcinoma. *Cancer* 1995; **76**: 1120-1125

7   Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna W, Byhardt R. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trails. *Int J Radiat Oncol Biol Phys* 1997; **37**: 745-751

8   Mandard A, Chasle J, Marnay J, Villedieu B, Bianco C, Roussel A, Elie H, Vernhes J. Autopsy findings in 111 cases of esophageal cancer. *Cancer* 1981; **48**: 329-335

9   Bosch A, Frias Z, Caldwell W, Jaeschke W. Autopsy findings in carcinoma of the esophagus. *Acta Radiol Oncol Radiat Phys Biol* 1979; **18**: 103-112

10 Gabrielsen T, Eldevik O, Orringer M, Marshall B. Esophageal carcinoma metastatic to the brain: clinical value and cost-effectiveness of routine enhanced head CT before esophagectomy. *Am J Neuroradiol* 1995; **16**: 1915-1921

11 Weinberg J, Suki D, Hanbali F, Cohen Z, Lenzi R, Sawaya R. Metastasis of esophageal carcinoma to the brain. *Cancer* 2003; **98**: 1925-1933

12 Perri F, Bisceglia M, Giannatempo G, Andriulli A. Cerebellar Metastasis as a unique presenting feature of gastric cancer. *J Clin Gastroenterol* 2001; **33**: 80-81

13 York J, Stringer J, Ajani J, Wildrick D, Gokaslan Z. Gastric cancer and metastasis to the brain. *Ann Surg Oncol* 1999; **6**: 771-776

14 Kim M. Intracranial involvement by metastatic advanced gastric carcinoma. *J Neurooncol* 1999; **43**: 59-62

15 Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. *Lancet* 2002; **360**: 1131-1135

16 Wang LD, Zheng S, Zheng ZY, Casson AG. Primary adenocarcinomas of lower esophagus, esophagogastric junction and gastric cardia: in special reference to China. *World J Gastroenterol* 2003; **9**: 1156-1164

17 Powell J, McConkey C. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* 1990; **62**: 440-443

18 Blot W, Devesa S, Kneller R, Fraumeni F. Rising increase of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265**: 1287-1289

19 Ko F, Lui J, Chen W, Chiang J, Lin T, Lin J. Risk and patterns of brain metastases in colorectal cancer: 27-year experience. *Dis Colon Rectum* 1999; **42**: 1467-1471

20 Cascino T, Leavengood J, Kemeny N, Posner J. Brain metastases from colon cancer. *J Neurooncol* 1983; **1**: 203-209

21 Wronski M, Arbit E. Resection of brain metastases from colorectal carcinoma in 73 patients. *Cancer* 1999; **85**: 1677-1685

22 Hammoud M, McCutcheon I, Elsouki R, Schoppa D, Patt Y. Colorectal carcinoma and brain metastasis: distribution, treatment, and survival. *Ann Surg Oncol* 1996; **3**: 453-463

23 Alden T, Gianino J, Saclarides T. Brain Metastases from colorectal cancer. *Dis Colon Rectum* 1996; **39**: 541-545

24 Batson O. The role of the vertebral veins in metastatic processes. *Ann Intern Med* 1942; **16**: 38-45

25 Burns F, Pfaff JJ. Vascular invasion in carcinoma of the colon and rectum. *Am J Surg* 1956; **92**: 704-710

26 Copeland E, Miller L, Jones R. Prognostic factors in carcinoma of the rectum and colon. *Am J Surg* 1968; **116**: 875-881

27 Hasegawa T, Kondziolka D, Flickinger J, Lunsford L. Stereotactic Radiosurgery for brain metastases from gastrointestinal tract cancer. *Surg Neurol* 2003; **60**: 506-515

28 Zorrilla M, Alonso V, Herrero A, Corral M, Puertolas T, Trufero J, Artal A, Anton A. Brain metastases from colorectal carcinoma. *Tumori* 2001; **87**: 332-334

29 Zulkowski K, Kath R, Liesenfeld S, Patt S, Hochstetter A, Behrendt W, Höffken K. Zerebrale metastasen bei kolorektalen karzinomen. *Med Klin* 2002; **97**: 327-334

30 Kasakura Y, Fujii M, Mochizuki F, Suzuki T, Takahashi T. Clinicopathological study of brain metastasis in gastric cancer patients. *Surg Today* 2000; **30**: 485-490

31 Nieder C, Niewald M, Schnabel K. Brain metastases of colon and rectum carcinomas. *Wien Klin Wochenschr* 1997; **109**: 239-243

32 Farnell G, Buckner J, Cascino T, O'Connell M, Schomberg P, Suman V. Brain metastases from colorectal carcinoma. The long term survivors. *Cancer* 1996; **78**: 711-716

33 D'Andrea G, Isidori A, Caroli E, Orlando E, Salvati M. Single cerebral metastasis from colorectal adenocarcinoma. *Neurosurg Rev* 2004; **27**: 55-57

34 Lutterbach J, Bartelt S, Ostertag C. Long-term survival in patients with brain metastases. *J Cancer Res Clin Oncol* 2002; **128**: 417-425

35 Lutterbach J, Cyron D, Henne K, Ostertag C. Radiosurgery followed by planned observation in patients with one to three brain metastases. *Neurosurgery* 2003; **52**: 1066-1073

36 Nieder C, Nestle U, Motaref B, Walter K, Niewald M, Schnabel K. Prognostic factors in brain metastases: should patients be selected for aggressive treatment according to recursive partitioning analysis (RPA) classes ? *Int J Radiat Oncol Biol Phys* 2000; **46**: 297-302

37 Lohr F, Pirzkall A, Hof H, Fleckenstein K, Debus J. Adjuvant treatment of brain metastases. *Semin Surg Oncol* 2001; **20**: 50-56

38 Schoeggl A, Kitz K, Reddy M, Zauner C. Stereotactic radiosurgery for brain metastases from colorectal cancer. *Int J Colorectal Dis* 2002; **17**: 150-155